Hodgkin's and Non-Hodgkin's Lymphomas

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INTRODUCTION

Lymphomas arise from lymphoid tissue throughout the body. They are distinguished from leukaemias, in which blood and bone marrow are inundated with white cells, although several disorders may have both leukemic and lymphomatous manifestations (Shimamoto *et al,* 1990; Banks, 1992; Foon *et al,* 1992). Hodgkin's disease (HD) is distinguished from other lymphomas mainly by the presence of giant Reed-Sternberg cells (Banks, 1990). The remaining non-Hodgkin's lymphomas (NHL) include a wide array of subtypes that generally can be separated into those with B cell or T cell lineage. The lineage of HD is uncertain, and re-examination of its relation to NHL has been recommended (Jaffe *et al,* 1992a; Variakojis and Anastasi, 1993). Hodgkin's and NHL may follow one another or be complicated by leukaemia as a result of therapy, natural history or shared aetiology (Greene and Wilson, 1985; Storm and Prena, 1985; Travis *et al,* 1992a,b).

The advent of immunophenotyping for frozen and even paraffin embedded tissue sections (Segal *et al,* 1991; Perkins and Kjeldsberg, 1993) and increasingly detailed cytogenetic studies (Ratech, 1993) have illuminated the connections between normal immune development and lymphoid malignancy.

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The emerging picture has forced major revisions in classification and nomenclature (Jaffe, 1990; Weisenberger, 1992).

Historical data suffer by comparison. In the 1950s, NHLs were classified as reticulosarcomas, lymphosarcomas and a few less common entities. At least six classification schemes arose subsequently, based in varying degrees on architectural, morphological, and clinical characteristics (Jaffe *et al*, 1992b). In 1982, a panel of experts devised a translation scheme, the NCI Working Formulation (Non-Hodgkin Lymphoma Pathologic Classification Project, 1982), grouping NHLs with similar prognosis and management. None of the schemes classifies NHL subtypes into the biological entities revealed by immunophenotyping and cytogenetics. Evaluation of the time trends in individual lymphoma subtypes would therefore require re-evaluation of older pathological specimens and application of modern classification.

Not all of the extensive, and continuing, redefinitions and reclassifications of lymphomas complicate the assessment of lymphoma trends over time, but many of them do. Some lymphomatous disorders may not have been recognized several decades ago; if fatal, another cause of death may have been recorded. Some leukaemias were misclassified as NHLs, and occasionally vice versa. Some NHLs were misclassified as HD, and occasionally vice versa. Only in recent years have B cell and T cell malignancies been distinguished, with B cell tumours apparently predominating in most parts of the world.

Although these changes in diagnostic practice have distorted the recorded trends in lymphoma, studies have been conducted to estimate the direction and degree of potential distortion (Glaser, 1990; Hasle and Mellemgaard, 1993). Although it is impossible to distinguish trends for many of the lymphoma subtypes now recognized, it is possible to disaggregate the trends, at least in the USA, using the subclassifications available in data routinely collected by tumour registries since the 1970s. Trends for HD and NHL can be separated from each other, with some adjustment for shifts between the two diagnoses. Hodgkin's can usefully be divided into nodular sclerosis and mixed cellularity subtypes; NHL can be categorized as diffuse or nodular, as nodal or extranodal, and according to the NCI Working Formulation histological subtypes.

TRENDS IN HODGKIN'S DISEASE AND NON-HODGKIN'S LYMPHOMA

Methods for Comparing International Time Trends

Age greatly affects the risk of developing lymphoma, so populations with different age distributions could have different unadjusted rates of lymphoma even if the rates were identical at each age. For international comparisons, rates are standardized to the World Standard to remove the simple effect of age differences. Comparisons based solely on USA data use rates standardized to the 1970 USA population.

The incidence and mortality rates shown in the figures compare age or calendar year on the x axis to the logarithm of the rate on the y axis. A straight line thus indicates a constant percentage change in incidence or mortality for each additional year.

Incidence rates recorded over the last 20 years are available from many registries around the world (Waterhouse *et al,* 1976, 1982; Devesa *et al,* 1987; Muir *et al,* 1987; Devesa and Fears, 1992; National Cancer Institute, 1992; Parkin *et al,* 1992; Surveillance, Epidemiology and End Results Program [SEER program] unpublished data). These data can be supplemented with incidence rates for longer periods in a few areas, albeit with greater distortion from changes in diagnostic practice.

International Trends in Incidence for Two Decades

Figure 1 shows slight changes in the incidence of HD among 20 populations as recorded by selected cancer registries around the world from the early 1970s to the mid-1980s. Age adjusted rates among men during the earlier period varied internationally from 0.8 per 100 000 person-years in Asia to 4 in North America (Table 1). In most of the 20 populations, incidence fell slightly; in the others, it rose slightly or showed no change, including Quebec, Warsaw, Israel, Bombay and Puerto Rico.

Around the world, women typically develop HD less frequently than men yet show parallel changes over time (Fig. 1). As shown in Table 2, there has been little change or slight decline in the occurrence of HD among most women. Decreases were reported for eight populations, increases for six and no change for the rest. Recent rates exceeded 2 per 100 000 person-years in Quebec, British Columbia, USA whites and Israel. Rates were less than 1 in Bombay, Osaka, Miyagi and Singapore, and rates were intermediate in the other registries. (In Fig. 1, rates in the Asian populations are shown on a scale from 0.3 to 6 among males and 0.2 to 4 among females; rates in all other populations are on a scale from 1 to 20.)

During the same period, NHL incidence increased dramatically in both sexes in all 20 populations (Fig. 2). Typically, age adjusted incidence rates rose by about 50% or more in less than two decades. By a wide margin, the absolute increase in NHL rates exceeded the decrease in HD rates among both men (Table 1) and women (Table 2).

Around 1970, NHL rates among men varied from less than 3 per 100 000 person-years in Warsaw, Bombay and Miyagi to more than 8 in USA whites and in British Columbia. In the Scandinavian registries, incidence rates were intermediate and similar to one another. A greater proportional increase in incidence (reflected in the slopes of the lines in Fig. 2) tended to occur in populations with initially lower rates. Nevertheless, all rates rose, and the ranking of geographic areas according to rate changed little.

The incidence of NHL in women also rose in all 20 registries (Table 2 and

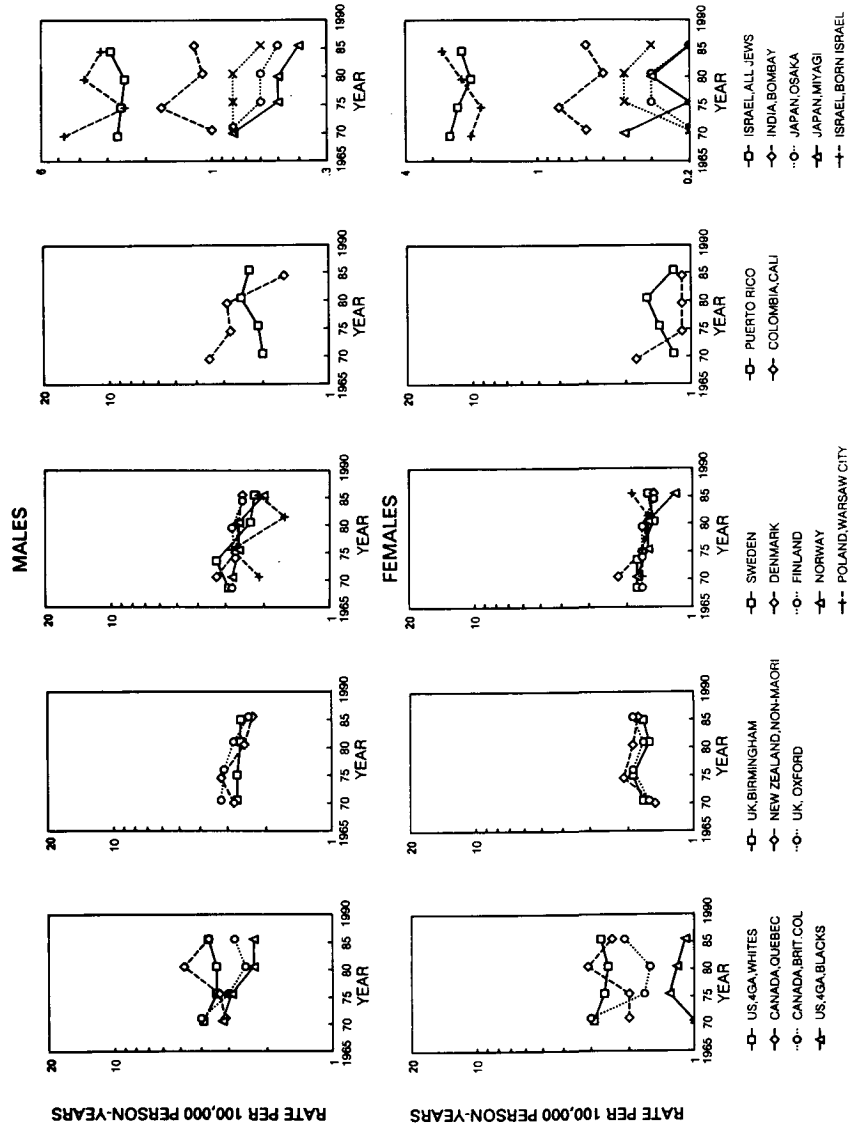

Fig. 1. Age adjusted incidence rates for Hodgkin's disease in 20 populations, 1968–1972 to 1983–1987. USA, 4GA = 4 geographical areas. (Sources: Waterhouse *et al*, 1976, 1982; Devesa *et al*, 1987; Muir *et al*, 1987; National Cancer Institute, 1992; Parkin *et al*, 1992; SEER program, unpublished data)

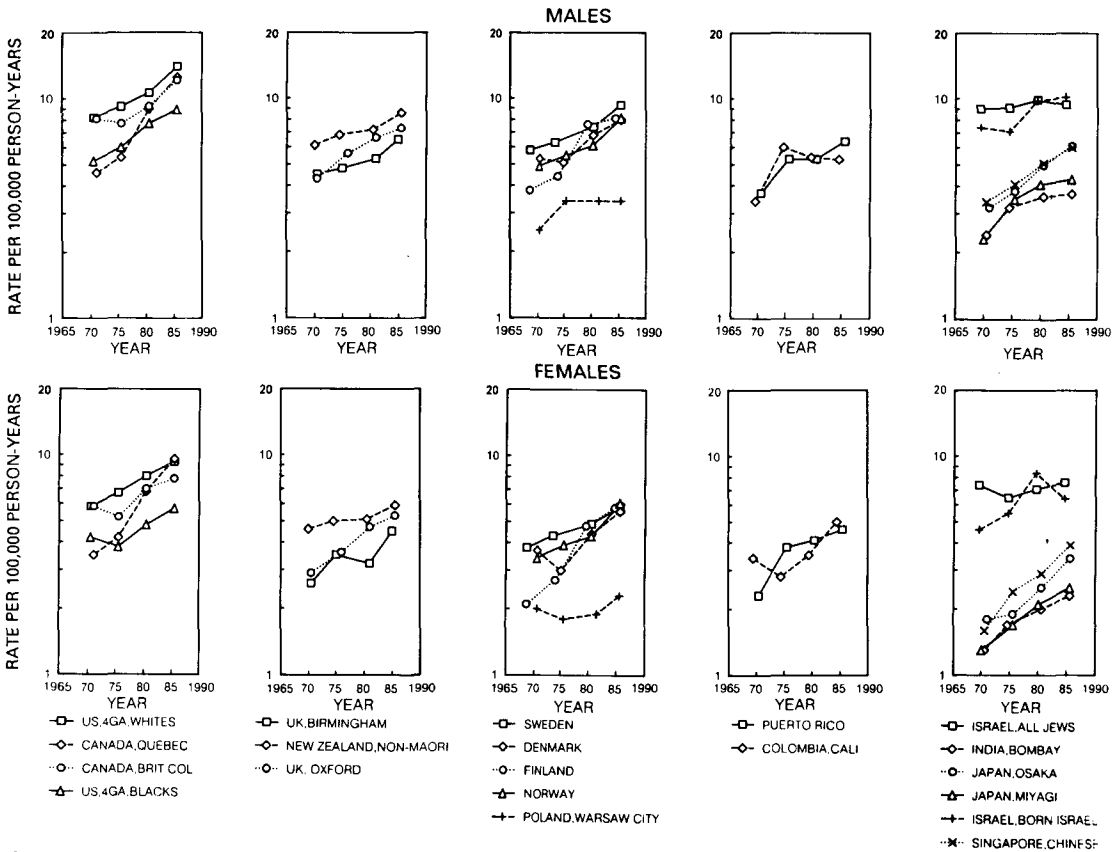

Fig. 2. Age adjusted incidence rates for non-Hodgkin's lymphoma in 20 populations, 1968–1972 to 1983–1987. USA, 4GA = 4 geographical areas. (Sources: Waterhouse *et al*, 1976, 1982; Devesa *et al*, 1987; Muir *et al*, 1987; National Cancer Institute, 1992; Parkin *et al*, 1992; SEER program, unpublished data)

TABLE 1. Age adjusted incidence rates[a] for Hodgkin's disease and non-Hodgkin's lymphoma among males in 20 populations, 1968–1972 and 1983–1987

	Incidence rate			
	HD		NHL	
	1968–1972[b]	1983–1987[c]	1968–1972	1983–1987
USA, 4 areas (white)	3.9	3.7	8.2	14.0
USA, 4 areas (black)	3.2	2.3	5.2	8.9
Quebec, Canada	3.1	3.7	4.6	12.5
British Colombia, Canada	4.0	2.8	8.1	12.1
Puerto Rico	2.0	2.3	3.7	6.4
Cali, Columbia	3.5	1.6	3.4	5.3
Birmingham, UK	2.7	2.6	4.5	6.5
Oxford, UK	3.2	2.4	4.3	7.3
New Zealand (non-Maori)	2.8	2.3	6.1	8.6
Sweden	2.9	2.2	5.8	9.3
Denmark	3.3	2.5	5.3	8.0
Finland	2.8	2.5	3.8	8.1
Norway	2.8	2.0	4.9	8.1
Warsaw, Poland	2.1	2.1	2.5	3.4
Israel (all Jews)	2.7	2.9	9.0	9.4
Israel (Jews born in Israel)	4.7	3.2	7.4	10.2
Bombay, India	1.0	1.2	2.4	3.7
Osaka, Japan	0.8	0.5	3.2	6.1
Miyagi, Japan	0.8	0.4	2.3	4.3
Singapore	0.8	0.6	3.4	6.0

Sources: Waterhouse *et al*, 1976; Devesa *et al*, 1987; National Cancer Institute, 1992; Parkin *et al*, 1992; SEER Program, unpublished data

[a]Per 100 000 person-years, age adjusted to world standard population

[b]Mid-point of the initial period varied from 1968 (Sweden, Finland) to 1971 (Osaka, Quebec, British Columbia), depending on data available

[c]Mid-point of the final period varied from 1984 to 1985

Fig. 2). In Quebec, Finland and Singapore, NHL incidence more than doubled in less than two decades. In British Columbia, Cali, New Zealand non-Maoris and Warsaw, incidence rose by less than 50%. In the other 13 populations, incidence rose 50–100%. Recent NHL incidence rates among women were highest in North America and lowest in Poland, India and Japan.

Long-term Trends in the USA

Incidence during the 1970s and 1980s in four geographical areas of the USA can be compared to data from 1947 to 1950, although the intervening years are not covered in all areas (Fig. 3). In the late 1940s, HD was diagnosed at the rate of 3.2 per 100 000 person-years and NHL at the rate of 6.9 among white men in the USA (Table 3). The incidence of HD rose to 4.2 around 1970 and has fallen slightly since, to reach 3.9 in the mid-1980s. By contrast, the incidence of NHL rose each decade, reaching 17.4 in the mid-1980s. This rate of increase is among the most rapid of all increases in cancer incidence to have

TABLE 2. Age adjusted incidence rates[a] for Hodgkin's disease and non-Hodgkin's lymphoma among females in 20 populations, 1968–1972 and 1983–1987

	Incidence rate			
	HD		NHL	
	1968–1972[b]	1983–1987[c]	1968–1972	1983–1987
USA, 4 areas (white)	2.9	2.7	5.8	9.3
USA, 4 areas (black)	1.0	1.1	4.2	5.7
Quebec, Canada	2.0	2.4	3.5	9.6
British Colombia, Canada	3.0	2.1	5.8	7.8
Puerto Rico	1.2	1.2	2.3	4.6
Cali, Columbia	1.8	1.1	3.4	5.0
Birmingham, UK	1.7	1.7	2.6	4.5
Oxford, UK	1.6	1.9	2.9	5.3
New Zealand (non-Maori)	1.5	1.8	4.6	5.9
Sweden	1.8	1.6	3.8	5.9
Denmark	2.2	1.5	3.7	5.6
Finland	1.7	1.5	2.1	5.8
Norway	1.8	1.2	3.4	6.1
Warsaw, Poland	1.7	1.9	2.0	2.3
Israel (all Jews)	2.5	2.2	7.4	7.6
Israel (Jews born in Israel)	2.0	2.7	4.6	6.4
Bombay, India	0.6	0.6	1.3	2.3
Osaka, Japan	0.2	0.2	1.8	3.4
Miyagi, Japan	0.4	0.2	1.3	2.5
Singapore	0.2	0.3	1.6	3.9

Sources: Waterhouse *et al,* 1976; Devesa *et al,* 1987; National Cancer Institute, 1992; Parkin *et al,* 1992; SEER Program, unpublished data

[a]Per 100 000 person-years, age adjusted to world standard population

[b]Mid-point of the initial period varied from 1968 (Sweden, Finland) to 1971 (Osaka, Quebec, British Columbia), depending on data available

[c]Mid-point of the final period varied from 1984 to 1985

been observed. Women in the USA showed parallel changes in age adjusted incidence over the past four decades. Thus, NHL incidence has been increasing for many years among men and women in the USA. For one of the areas, Connecticut, data collected continuously since 1935 show that rates have been rising steadily for five decades (Holford *et al,* 1992; Zheng *et al,* 1992).

Long term increases in the observed incidence of disease can reflect improved diagnosis rather than more frequent occurrence. If causes of death are reasonably well understood and recorded, mortality trends may provide more compelling evidence for a true increase. For NHL, age adjusted mortality has been rising steadily for four decades (Fig. 4); this is consistent with increased occurrence, although diagnostic changes cannot be excluded entirely. By contrast, HD mortality has shown dramatic reductions with the passage of time (Devesa *et al,* 1987; Hooper *et al,* 1992). Therapy for HD has become so effective during the last two decades that three fourths of cases now can be cured (Urba and Longo, 1992). Thus, the pattern of slight decrease in HD incidence since 1970 (Fig. 3) has been amplified by improved survival rates to produce a marked decline in mortality rates (Fig. 4).

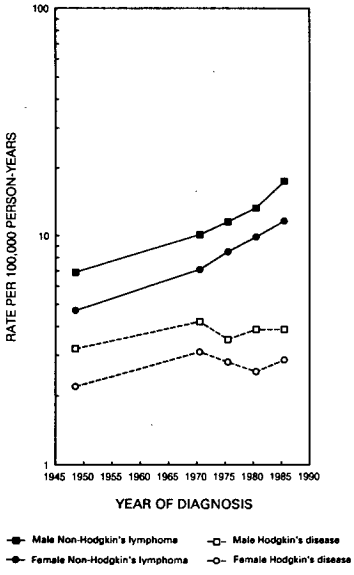

Fig. 3. Age adjusted incidence rates for Hodgkin's disease and non-Hodgkin's lymphoma among whites in four geographical areas of the USA, 1947–1950 to 1984–1988. (Sources: Devesa *et al*, 1987; National Cancer Institute, 1992; SEER program, unpublished data)

Trends by Age Group

Diagnosis of NHL and death attributed to it appear to be rising in both sexes around the world, but they are not rising in parallel for all age groups. The long term trend lines in the USA show a fan shaped pattern when separated by age at diagnosis (Fig. 5). Among men and women aged 25–44, incidence rose by more than half over the 40 year period, and at ages 45–65, it doubled, whereas at older ages, it tripled.

Changing age specific rates may reflect the introduction of a new aetiological agent that affects particular birth cohorts. As shown in Fig. 6, the NHL mortality risks faced by successive birth cohorts in the USA show no clear evi-

TABLE 3. Age adjusted incidence rates[a] for Hodgkin's disease and non-Hodgkin's lymphoma among whites in four geographical areas of the USA, 1947–1950 to 1984–1988

	Incidence rate			
	male HD	female HD	male NHL	female NHL
1947–1950	3.2	2.2	6.9	4.7
1969–1971	4.2	3.1	10.1	7.1
1974–1978	3.5	2.8	11.5	8.5
1979–1983	3.9	2.6	13.3	9.9
1984–1988	3.9	2.9	17.4	11.6

Sources: Devesa *et al*, 1987; National Cancer Institute, 1992; SEER program, unpublished data
[a]Per 100 000 person-years, age adjusted to 1970 USA standard

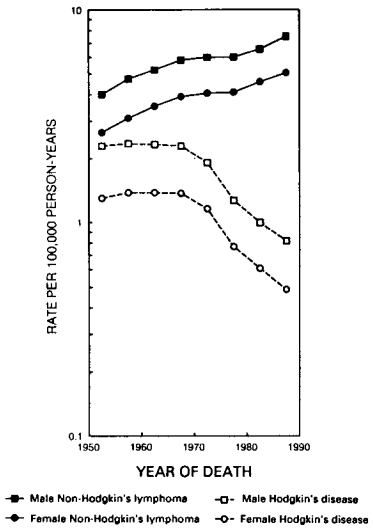

Fig. 4. Age adjusted mortality rates for Hodgkin's disease and non-Hodgkin's lymphoma among whites in the USA, 1950–1954 to 1985–1989. (Sources: Devesa *et al*, 1987; National Center for Health Statistics, unpublished data)

dence of such a sudden exposure. If any pattern emerges, it may be that the factors responsible for the increases among people born in the late 1800s have not continued to elevate rates among people born in this century. Analysis of 50 year trends in Connecticut incidence data also reveals no clear basis for viewing the rates as changing with birth year rather than with calendar time of diagnosis (Holford *et al*, 1992). It seems likely that the disproportionate increase in NHL among older people at least partly reflects differential improvements in diagnosis.

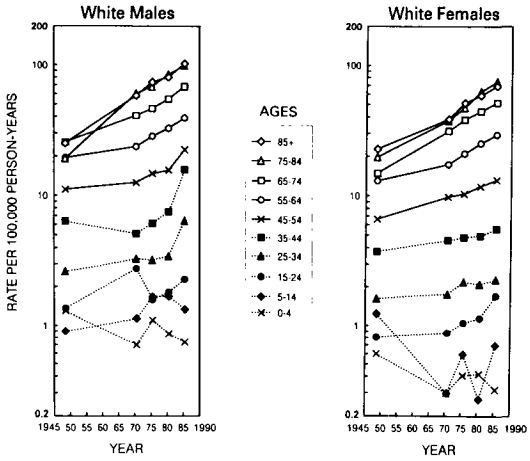

Fig. 5. Age specific incidence rates for non-Hodgkin's lymphoma among whites in four geographical areas of the USA, 1947–1950 to 1985–1988. (Sources: Devesa *et al*, 1987; National Cancer Institute, 1992; SEER program, unpublished data)

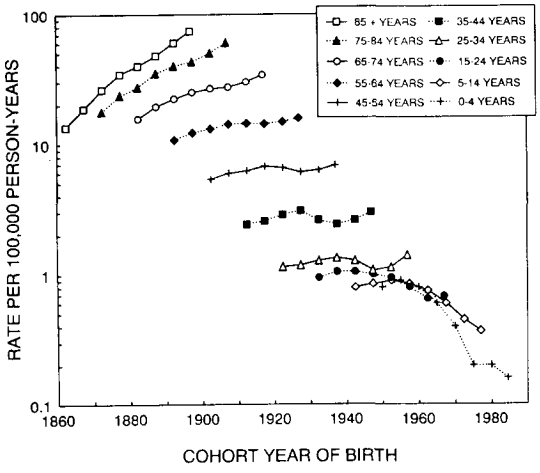

Fig. 6. Age specific mortality rates for non-Hodgkin's lymphoma among whites by cohort year of birth. (Sources: De vesa *et al*, 1987; National Center for Health Statistics, unpublished data)

The fan shaped pattern of age specific time trends in the USA is less dramatic over the two decade span than the four decade span, and incidence data from the most recent years show the emergence of an additional epidemic of AIDS related NHL among young and middle aged adults, especially in men (Devesa and Fears, 1992). The trend of greater increases in NHL at older ages will be reversed as the full impact of human immunodeficiency virus (HIV) infection is felt (Gail *et al*, 1991). It is noteworthy that the upward trends in NHL incidence accompanying AIDS first surfaced among young adult males in San Francisco (Biggar and Rabkin, 1992).

International time trends for NHL over two decades show the fan shaped pattern of age specific incidence rates for only a few countries, notably some of the industrialized societies (Waterhouse *et al*, 1976, 1982; Muir *et al*, 1987; Parkin *et al*, 1992). Many registries report upward trends in nearly all age groups, but the rate of increase bears no simple relation to age. In the UK, as in the USA, increases have been more pronounced among older people, both men and women. In Sweden and Israel, rates rose proportionally in all age groups. In Bombay, rates rose faster in older men but slower in older women. In Puerto Rico and Quebec, patterns also differed between men and women.

Trends in HD also vary by age at diagnosis, in a fashion that may shed light on the reasons for the overall time trends. Table 4 shows a complex pattern of age specific incidence changing over time in the USA. At ages 15–24, incidence has risen since the late 1940s. At ages 25–34, incidence rose from the late 1940s to a plateau in the early 1970s. At ages 55–64, incidence has been steadily declining, whereas incidence at ages over 65 rose between the late 1940s and the early 1970s and declined thereafter. A similar complex shift occurred among females.

A clearer picture of the changing age specific incidence of HD emerges

TABLE 4. Age specific incidence rates for Hodgkin's disease in four geographical areas of the USA, 1984–1988, white males and white females

Year	Age specific incidence rate [a]									
	0–4	5–14	15–24	25–34	35–44	45–54	55–64	65–74	75–84	85+
White male										
1947–1950	0.00	1.26	2.89	2.83	3.70	4.85	6.94	5.80	5.74	0.00
1969–1971	0.10	0.95	4.81	5.62	4.20	4.50	5.94	7.86	13.04	9.70
1974–1978	0.00	0.96	4.76	5.11	3.34	3.26	4.66	6.27	8.14	6.98
1979–1983	0.00	1.29	5.47	5.40	3.98	3.66	4.76	6.91	7.41	7.32
1984–1988	0.00	1.36	5.81	5.47	4.12	4.02	4.63	5.18	6.80	6.97
White female										
1947–1950	0.00	0.61	2.17	3.42	2.83	2.03	4.68	3.83	3.01	0.00
1969–1971	0.20	0.91	4.74	3.05	2.69	2.55	3.91	8.17	7.44	3.90
1974–1978	0.07	1.08	5.11	4.21	2.09	2.17	2.72	3.85	4.80	8.11
1979–1983	0.00	0.94	4.74	4.51	2.10	1.67	1.93	3.73	4.17	3.41
1984–1988	0.00	0.81	6.03	4.65	2.74	1.48	2.85	3.28	3.69	2.74

Sources: Devesa *et al*, 1987; National Cancer Institute, 1992; SEER Program, unpublished data
[a]Per 100 000 person-years

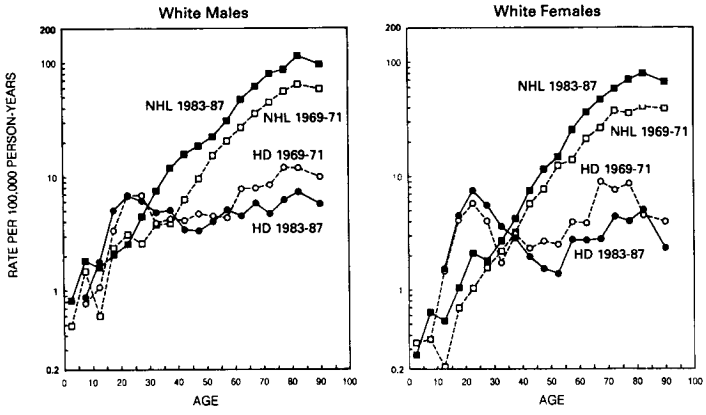

Fig. 7. Age specific incidence rates for Hodgkin's disease and non-Hodgkin's lymphoma among whites in four geographical areas of the USA, 1969–1971 and 1983–1987. (Sources: Devesa *et al*, 1987; National Cancer Institute, 1992; SEER program, unpublished data)

from considering the age incidence curve in two calendar periods, 1969–1971 and 1983–1987 (Fig. 7). In both periods, the age incidence curves are bimodal, an unusual shape that prompted MacMahon (1957, 1966) to suggest that HD encompasses two separate diseases, with an infectious aetiology for cases occurring at young ages. The bimodality appears now to be more prominent in females than in males. Since 1970, incidence rates in the USA under age 40 (peaking around 25) have risen, whereas the rates at older ages have fallen (Fig. 7). Connecticut data spanning five decades suggest that the increases among young people have been occurring for many years (Fig. 8). Among older people, rates generally increased over the long term but declined slightly in recent years (Roush *et al*, 1987). These data also show more prominent bimodality among women. Among young adults, the recent rates in females have been as high or higher than in males, whereas among older people, the rates are lower in females than males.

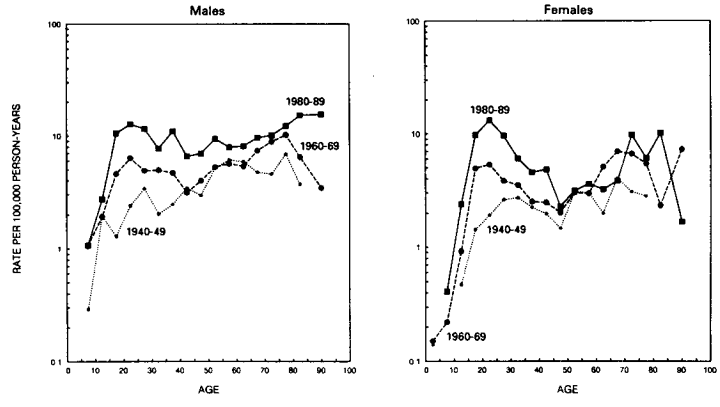

Fig. 8. Age specific incidence rates for Hodgkin's disease in Connecticut, 1940–1949, 1960–1969, 1980–1989. (Source: Connecticut Tumour Registry, unpublished data)

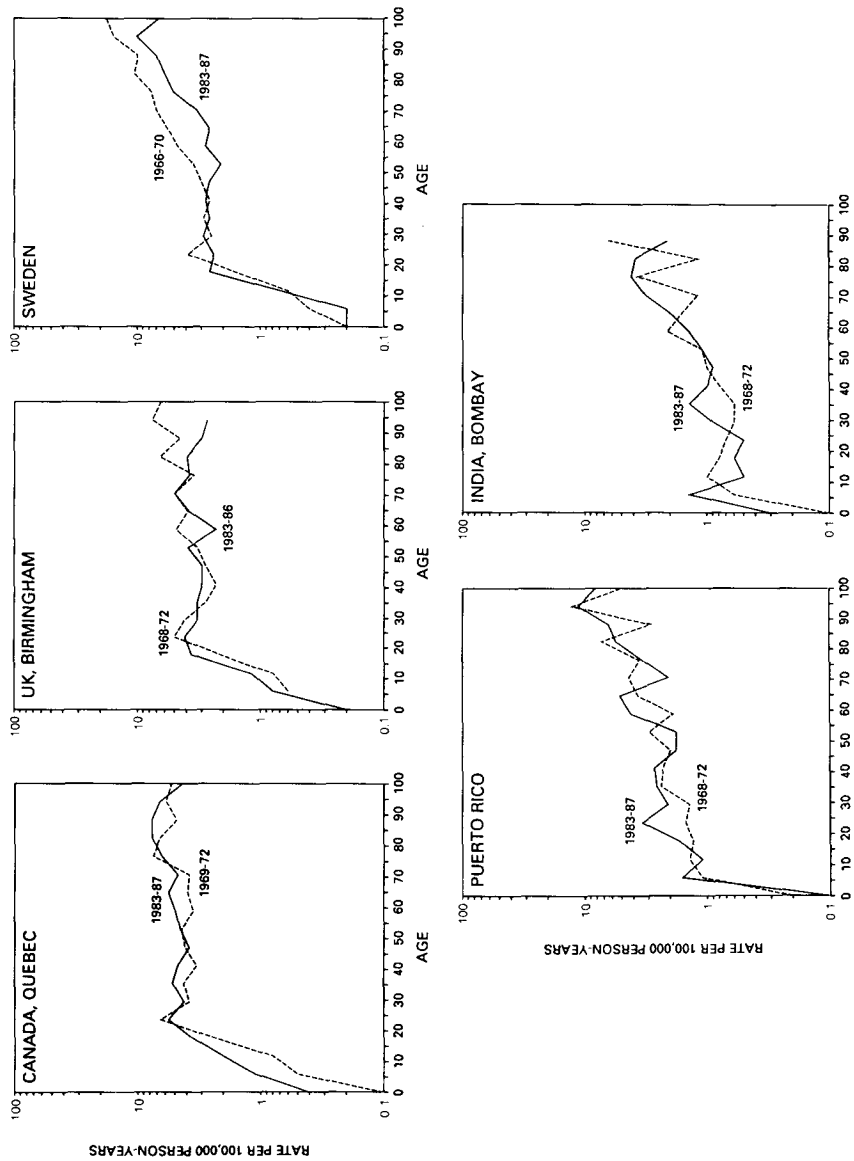

Fig. 9. Age specific incidence rates for Hodgkin's disease among males in five populations, circa 1970 and 1985. (Sources: Waterhouse *et al*, 1976; Parkin *et al*, 1992)

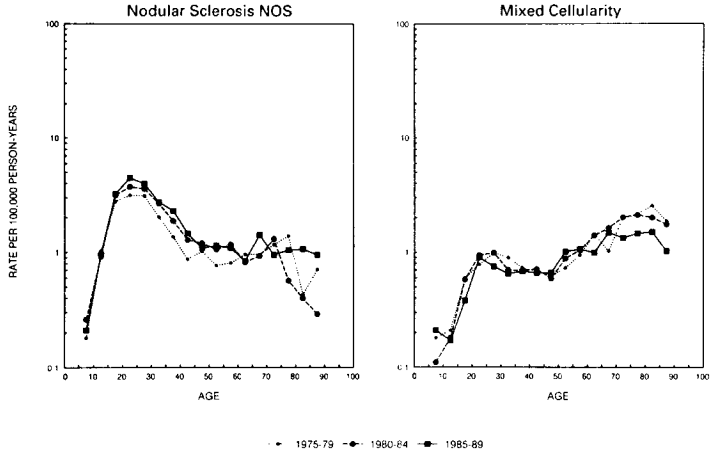

Fig. 10. Age specific incidence rates for two histological subtypes of Hodgkin's disease among whites, SEER program in the USA, 1975–1979 to 1985–1989. (Sources: National Cancer Institute, 1992; SEER program, unpublished data)

To a lesser extent than seen in the USA, the young adult peak of HD is seen in other industrialized areas, such as Quebec, Birmingham and Sweden (Fig. 9). In Sweden, rates fall slightly after the young adult peak and rise thereafter, whereas they plateau in Quebec and Birmingham. In these three populations, incidence has risen slightly in the young and fallen slightly in the old in recent years. In less developed countries, age specific incidence of HD follows a different pattern (Correa and O'Conor, 1971). For example, in Puerto Rico and Bombay, incidence rises steeply in childhood to exceed rates in the industrialized countries (Fig. 9). No distinct peak occurs in young adulthood, and incidence continues to rise with age. No clear time trends in the age specific rates are as yet evident.

Trends by Subtype

At younger ages, HD cases of the nodular sclerosing subtype predominate, whereas those of the mixed cellularity subtype predominate at older ages (Glaser, 1986; Alexander *et al*, 1991a). Figure 10 shows that nodular sclerosing HD rose from 1975–1979 to 1985–1989, whereas mixed cellularity HD fell in nine areas of the USA. Extranodal HD occurs rarely, typically 1% as often as nodal disease. There was a suggestion of decline in extranodal HD in the SEER program from 1974–1978 to 1984–1988.

Incidence trends for NHL also show some differences when separated by histological subtype and other characteristics, although not as clearly as HD. Both high grade and low grade NHL incidence has risen in Yorkshire, England (Cartwright, 1992), and both nodal and extranodal NHL have increased in the USA (Table 5). Extranodal NHL accounts for less than one quarter of NHL but has risen faster than nodal disease. Extranodal sites typically involve the stomach, small intestine, skin and brain (Salhany and Pietra, 1993). (In earlier

TABLE 5. Age adjusted incidence rates for nodal and extranodal sites of non-Hodgkin's lymphoma, SEER program, 1974–1978 to 1984–1988

	Cases	Rates[a]				% Change	
	1974–1978	1974–1978	1979–1983	1984–1988	Absolute change	total	per year
White males							
nodal	3521	8.9	10.5	12.5	3.6	40	2.5
extranodal	957	2.4	2.7	4.1	1.7	71	3.7
White females							
nodal	3393	6.8	7.8	8.6	1.8	26	1.7
extranodal	882	1.7	1.9	2.6	0.9	53	3.0
Black males							
nodal	187	5.6	6.7	7.6	2.0	36	2.2
extranodal	47	1.4	2.6	2.9	1.51	107	5.0
Black females							
nodal	150	3.8	4.9	5.2	1.4	37	2.2
extranodal	27	0.6	1.5	1.7	1.1	183	6.9

Source: Devesa and Fears, 1992
[a]Per 100 000 person-years, age adjusted using 1970 USA standard

years, some of these extranodal lymphomas may have been classified as cancer of the site of occurrence rather than as lymphomas, even if lymphoma was specified.) Non-Hodgkin's lymphoma arising in the brain has risen four times as rapidly as extranodal NHL as a whole (Table 6). Part of the recent increase reflects infection by HIV, but the upward trend began earlier. The increase in

TABLE 6. Age adjusted incidence rates for extranodal non-Hodgkin's lymphoma by site of origin, SEER program, 1974–1978 to 1984–1988

	Cases	Rates[a]			Change	
	1984–1988	1974–1978	1979–1983	1984–1988	absolute	%
Stomach	699	0.41	0.42	0.61	0.20	49
Skin	612	0.33	0.49	0.55	0.22	67
Brain and other nervous system	367	0.09	0.15	0.31	0.22	244
Small intestine	314	0.18	0.20	0.28	0.10	56
Colon and rectum	184	0.10	0.09	0.16	0.06	60
Oral[b]	149	0.08	0.09	0.12	0.04	50
Soft tissue	140	0.08	0.09	0.12	0.04	50
Eye	132	0.05	0.06	0.12	0.07	140
Thyroid	130	0.07	0.10	0.12	0.05	71
Salivary gland	119	0.06	0.07	0.10	0.04	67
Lung	111	0.07	0.08	0.10	0.03	43
All sites	3640	1.98	2.25	3.20	1.22	62

Source: Devesa and Fears, 1992
[a]Per 100 000 person-years, age adjusted using 1970 USA standard
[b]Excludes lip, salivary glands, nasopharynx

TABLE 7. Age adjusted incidence rates for nodular and diffuse types of non-Hodgkin's lymphoma, SEER program, 1978–1981 to 1986–1988

	Cases	Rates[a]				% Change	
	1978–1981	1978–1981	1982–1985	1986–1988	Absolute change	total	per year
Nodular	1959	2.3	2.5	2.6	0.3	13	1.9
Diffuse	6906	7.9	9.1	10.3	2.4	30	3.6
Other	294	0.3	0.4	0.5	0.2	67	5.2
Total	9159	10.5	12.0	13.4	2.9	28	3.4

Source: Devesa and Fears, 1992
[a]Per 100 000 person-years, age adjusted using 1970 USA standard

NHL of the central nervous system warrants investigation, although it contributes only slightly to the long term NHL trends.

About three fourths of NHL are diffuse tumours, whereas most others are nodular (Table 7). Both types have increased in incidence, with the diffuse pattern increasing somewhat faster. In the USA, incidence of NHL at all grades increased, especially high grade cancers (Table 8). AIDS associated NHL often represents high grade tumours, which may continue to grow faster than other Working Formulation categories. The apparent drop in incidence of diffuse small cleaved cell tumours probably represents a change in diagnostic practice.

IMPACT OF CHANGES IN DIAGNOSTIC PRACTICE

Lymphomas versus Other Diseases

Patients discharged from USA hospitals with NHL as the primary diagnosis in 1970–1971 had a different cancer cause of death recorded 12% of the time, commonly HD or gastrointestinal cancer (Percy *et al*, 1981). For those with NHL on the death certificate, 83% were so diagnosed in a hospital. For HD, the corresponding figures were 8% and 87%. For both cancers, the percentages were better than average.

Distinguishing lymphomas from leukaemias occasionally may be difficult or arbitrary, for example chronic lymphocytic leukaemia versus low grade NHL or acute lymphoblastic leukaemia versus lymphoblastic lymphoma. Some data sources group together certain leukaemias with lymphomas (Martinsson *et al*, 1992). In addition, more thorough detection of tumour cells in blood and bone marrow may have led some cases that would have been diagnosed as NHL decades ago to be called leukaemia in recent years. Trends in multiple myeloma and leukaemia are discussed in detail elsewhere in this volume, but clearly the recent increase in NHL finds no commensurate decrease in the

TABLE 8. Age adjusted incidence rates for non-Hodgkin's lymphoma by the NCI Working Formulation, SEER program, 1978–1981 to 1986–1988

	Cases	Rates[a]			Absolute	% Change	
	1978–1981	1978–1981	1982–1985	1986–1988	change	total	per year
Low grade	2398	2.8	3.1	3.4	0.6	21	2.8
A: small, lymphocytic	859	1.0	1.1	1.3	0.3	30	4.0
B: follicular, small cleaved	1139	1.3	1.4	1.3	0.0	0	–
C: follicular, mixed[b]	400	0.5	0.6	0.7	0.2	40	6.3
Intermediate	4626	5.3	5.6	6.1	0.8	15	2.0
D: follicular, large cell	169	0.2	0.3	0.4	0.2	100	8.3
E: diffuse, small cleaved	1506	1.7	1.2	0.9	−0.8	−47	−8.2
F: diffuse, mixed	564	0.6	0.9	0.9	0.3	50	4.4
G: diffuse, large cell	2387	2.7	3.2	4.0	1.3	48	5.2
High grade	447	0.5	1.1	1.6	1.1	220	14.8
H: large cell, immunoblastic	168	0.2	0.6	0.8	0.6	300	18.1
I: lymphoblastic	75	0.1	0.2	0.2	0.11	100	12.2
J: small non-cleaved; Burkitt's	204	0.2	0.4	0.6	0.4	200	11.6
Unclassified	1688	1.9	2.1	2.3	0.4	21	2.6
Total	9159	10.5	12.0	13.4	2.9	28	3.4

Sources: Devesa and Fears, 1992
[a]Per 100 000 person-years, age adjusted using 1970 USA standard
[b]Small cleaved and large cell

related tumours. Thus, NHL incidence rose from about 7 to about 15 per 100 000 person-years among white men in the USA in three decades, whereas multiple myeloma and leukaemia increased from 1.5 and 11 to 4 and 13, respectively (Devesa *et al,* 1987).

Hodgkin's versus Non-Hodgkin's Lymphomas

Although not nearly enough to explain NHL trends, misdiagnosis of NHL as HD has occurred in the past for various reasons. There is a genuine zone of overlap affecting a few entities that share some but not all characteristics of HD and NHL (Banks, 1990; Tosi *et al,* 1992), and HD and NHL can occasionally coexist, as in nodular lymphocyte predominant HD together with large cell lymphoma (Harris, 1992). These cases would not necessarily have been classified differently over time and are rare in any event. Nomenclature and classification have also changed for some entities, for example peripheral T cell lymphomas and anaplastic lymphomas (Banks, 1992). Furthermore, tumours with Reed-Sternberg cells but surrounded by neoplastic lymphocytes were reclassified as NHL about 20 years ago (Banks, 1992). In addition, some misclassification has occurred due to absent or erroneous histological evaluation.

To estimate the extent of misclassification by age, time period and subtype, Glaser and Swartz (1990) reviewed slides from a large series of HD patients enrolled in clinical treatment studies in the USA. Data excerpted from their study (Table 9) show that 83% of the cases originally diagnosed as HD in 1969–1974 were deemed to be HD after review, and most of the 17% misdiagnosed actually were NHL. This overdiagnosis of HD occurred only 5% of the time among cases from 1980 to 1984. The error rate was similar in men and women, but much greater in the elderly than in the young and among cases of mixed cellularity. Only half of the cases diagnosed as mixed cellularity HD in 1969–1984 were confirmed as HD; similarly, fewer than half of patients aged 65 or older were correctly diagnosed during 1969–1974. Even when adjusted for diagnostic error, the incidence of nodular sclerosing HD rose in the USA from 1975–1979 to 1980–1984, whereas the incidence of mixed cellular HD fell slightly (Glaser and Swartz, 1990).

Misdiagnosis of NHL as HD may have been even more common before the 1970s. If the error rate around 1950 were 30% and if 60% of the erroneously diagnosed were NHL, then 0.6 white male cases per 100 000 person-years might have been misallocated between HD and NHL in the USA in 1947–1950 (Hartge and Devesa, 1992). This addition would have a negligible impact on the steep trend in NHL.

Martinsson and coworkers (1992) examined all 744 HD, NHL and chronic lymphocytic leukaemia cases from one Swedish county in 1969–1987 and histopathologically diagnosed 639 of them. Almost one half of cases registered as HD in 1969–1978 were reclassified as NHL compared to one fifth in 1979–1987. Before correction, registered NHL cases would have been missing those

TABLE 9. Percentage of diagnoses of Hodgkin's disease among whites confirmed by pathology slide review by age, time period and histological subtypes, Repository Center for Lymphoma Clinical Studies, 1969–1974 and 1980–1984

Age	Time period[a]		Histological subtype[b]	
	1969–1974	1980–1984	nodular sclerosing	mixed cellularity
0–14	85	100	79	28
15–24	92	99	87	48
25–34	92	95	88	61
35–44	84	95	80	59
45–54	78	98	73	55
55–64	60	92	66	43
65–74	51	79	68	47
≥75	33	83	68	25
All	83	95	83	52

Source: Glaser and Swartz, 1990
[a]All subtypes combined
[b]All years combined

cases incorrectly called HD and a similar number that were not reported routinely to tumour registries, some discovered at autopsy. Incorrect assignment of NHL as a diagnosis also occurred, but about 40% as often as missed diagnoses.

The discovery of HD or NHL at autopsy could also be changing over time. Hasle and Mellemgaard (1993) studied the 2.4% of HD cases under age 70 in Denmark that were found at autopsy. Most had no concurrent disease. Discovery of HD at death never occurred under age 50 and mostly happened over age 65. Autopsy rates have fluctuated over time and vary internationally, but autopsy findings do not appear to be a major source of NHL or HD diagnoses. Cartwright (1992) histologically reviewed all lymphomas, nodal undifferentiated carcinomas and nodal benign hyperplasias in Yorkshire, UK from 1963–1967 to 1984–1988. During that period, corrected NHL incidence increased in all age groups, especially in the old.

Table 10 shows that nearly all NHL diagnoses in the SEER program in the USA are confirmed by histology review and have been for two decades. Although NHL once may have gone undiagnosed, there is no evidence that such tumours now are overdiagnosed.

Subtypes of Non-Hodgkin's Lymphoma

Apart from changes in lymphoma diagnoses on the border of HD and NHL, the extensive revisions of NHL subtyping affect the interpretation of trends in other ways. Pathologists have redesignated as NHL a few entities once considered benign (Banks, 1991). Lymphoid tissue in mucosa can give rise to low grade B cell lymphomas, now called mucosa associated lymphoid tumours

TABLE 10. Percentage of non-Hodgkin's lymphoma cases with microscopic confirmation by race, sex and age, SEER program, 1974–1978 and 1984–1988

Age	Percentage confirmed		
	1969–1974	1980–1984	1984–1988
Race and sex			
White males	98.2	98.4	97.9
White females	97.7	97.6	97.9
Black males	97.4	98.0	97.5
Black females	97.7	97.7	96.0
Age group (among white males)			
0–14 years	98.6	100.0	99.2
15–34 years	98.5	97.7	98.1
35–54 years	99.2	99.2	98.0
55–74 years	98.5	98.8	98.6
≥75 years	96.2	96.7	96.1

Source: Devesa and Fears, 1992

(MALT) but once called benign extranodal pseudolymphomas (Banks, 1992). Similarly, angioimmunoblastic lymphadenomas now commonly are described as T cell lymphomas.

Changes in diagnostic categories preclude estimation of subtype specific NHL trends. Mortality rates in the USA from 1950 to 1965 suggested disproportionate increases in reticulum cell sarcoma or histiocytoma lymphoma (Cantor and Fraumeni, 1980). Incidence rates from 1969–1971 and 1973–1977 did not show continuation of that trend (Cutler and Young, 1975; Young *et al*, 1981), but patterns thereafter cannot be discerned because of changed nomenclature. Even within a particular scheme and with current pathology specimens, classification into histological subtypes remains uncertain. A review of histological diagnoses of NHL (Dick *et al*, 1987) showed high agreement (93%) with an original diagnosis as NHL, but low agreement (55%) with the original classification into the ten NCI Working Formulation subtypes. Even the four experienced pathologists on the reviewing panel disagreed with each other 40% of the time.

IMPACT OF CHANGES IN RISK FACTORS

Hodgkin's Disease

The causes of HD are not clear, but many scientists have been intrigued by the model offered by MacMahon (1957) that a virus with low infectivity causes the early age peak. Clustering of HD cases has been reported (Glaser, 1990; Alexander *et al*, 1991b), although the epidemiological evidence is still inconclusive. A viral origin has been suggested by the association of HD with certain childhood environments, such as small family size and uncrowded conditions, that could reduce or delay infections, as in paralytic poliomyelitis (Gutensohn and Cole, 1981). Epstein-Barr virus (EBV) remains the leading candidate, since infectious mononucleosis increases risk of HD (Serraino *et al*,

1991), EBV antibody titres in sera collected well before HD diagnosis indicate heightened replication of EBV (Mueller *et al,* 1992) and the EBV genome is found to be integrated in HD cells (Weiss *et al,* 1989). On the other hand, EBV occurs widely, is found in cells other than Reed-Sternberg cells in HD (Khan *et al,* 1992) and could be a passenger virus. Mueller (1991) has proposed that latent infection with EBV chronically stimulates the immune system until any of a variety of clonal rearrangements occur, lymphokine production changes, other antigens elicit abnormal responses and HD develops.

Could changing exposure patterns to EBV explain HD trends? Perhaps age at EBV infection has changed (eg with more late infections in industrialized countries contributing to the increases observed among younger people). On the other hand, EBV in situ hybridization studies show EBV in mixed cellularity HD more than in nodular sclerosing HD and in children or adults older than 50 more than in younger adults (Khan *et al,* 1993). On the basis of current data, age at EBV exposure would not easily explain the decreasing rates for older people and mixed cellularity HD or the increasing rates for young adults and nodular sclerosing HD .

Occupational risk factors for HD may include exposures to solvents, wood dust and agricultural chemicals (Franceschi *et al,* 1991; Grufferman and Delzell, 1984). Trends in the prevalence of these exposures have not been linked to HD trends. Despite early reports, tonsillectomy and appendectomy appear not to increase risk (Gledovic and Radovanovic, 1991). Teachers and physicians, despite potential contact with HD patients, apparently do not have increased HD risk (Grufferman and Delzell, 1984).

Non-Hodgkin's Lymphoma

If changing diagnostic practice cannot account for the startling rise in NHL, perhaps changing exposure patterns can. Risk factors for NHL include several viruses, immunosuppressive states, family history and several occupations, including farmers and other groups with high exposures to herbicides and pesticides.

It is clear that HIV infection, the cause of AIDS, has contributed to the rise in NHL incidence in recent years. As HIV infection increases, the incidence of lymphoma will rise further to account for a major share of NHL throughout the world (Gail *et al,* 1991; Obrams and Grufferman, 1991; Rabkin *et al,* 1991, 1992; Serraino *et al,* 1992). Cumulative incidence of NHL among the HIV infected population is now 5–10% over a decade (Obrams and Grufferman, 1991). Current estimates of NHL cases among the HIV infected in the USA (Karon *et al,* 1992) accord with predictions from earlier data made by Gail *et al* (1991). Some evidence is emerging that HIV infection also leads to HD (Serrano *et al,* 1990), although less than 10% as often as NHL (Hessol *et al,* 1992). Despite its large looming impact, this relatively new virus cannot account for the upward NHL trend seen for at least two and possibly five decades around the world.

Another retrovirus, human T lymphotropic virus type I (HTLV-I), induces a specific form of lymphoma, called adult T cell leukaemia-lymphoma (ATL) that typically has a worse prognosis than other T cell lymphomas (Matsuzaki *et al,* 1990; Shimamoto *et al,* 1990; Shih *et al,* 1992). Perhaps 1% of those infected with HTLV-I will develop ATL before age 40 and 4% by age 80 (Kondo *et al,* 1989, Mueller *et al,* 1992). Apparently, HTLV-I is an old, stable virus with fairly low infectivity that now accounts for a small fraction of lymphomas in the USA and most likely accounts for none of the time trends. In high risk areas of the world, such as Japan and the Caribbean, the virus appears to be transmitted early in life and may also be spread by sexual activity, parenteral drug use and blood transfusion.

Generally considered the necessary cause of Burkitt's lymphoma, EBV may also play a part in other forms of NHL (Mueller *et al,* 1991), perhaps in concert with other viruses including HIV (Ott *et al,* 1992). It appears to be involved in lymphoma that arises in a variety of immunodeficiency disorders, probably interacting with immunological and genetic mechanisms. It has been suggested that EBV leads to a polyclonal expansion of non-malignant cells, with a second event, perhaps proto-oncogene activation, selecting a clone that leads to NHL (Longo *et al,* 1993). If this model is correct, ubiquitous EBV infection may have little part to play in NHL trends unless changes have occurred in the timing of infection or in co-factors.

A striking predisposition to NHL has been documented in rare genetic syndromes characterized by depressed immune function, such as Wiskott-Aldrich syndrome, ataxia–telangiectasia, common variable immunodeficiency and the X linked lymphoproliferative syndrome (Filipovich *et al,* 1992). In these immunodeficiency disorders, the further study of specific defects involved in immune regulation may uncover critical or unifying features of lymphomagenesis. Genetic risk explains none of the time trends, although environmental features may be especially apparent among families with multiple cases of lymphoproliferative or haematopoietic malignancies (Fraumeni *et al,* 1975; Pottern *et al,* 1991; Linet and Pottern, 1992).

Like genetic immunodeficiency, immunosuppressive therapy leads to enormous increases in NHL risk, but only when the immunosuppression is profound, as among transplant recipients (Penn, 1991; Hoover, 1992; Kinlen, 1992). Since medications, viruses and genes that lead to severe immunosuppression can cause lymphomas, can mild immunosuppression do so as well? Rheumatoid arthritis patients have an increased risk of NHL, although it is difficult to disentangle the effects of immunosuppressive drugs and immunostimulatory mechanisms associated with autoimmune disease (Kinlen *et al,* 1979; Hakulinen *et al,* 1985; Kinlen, 1985, 1992; Symmons, 1985, 1988; Doody *et al,* 1992; Gridley *et al,* 1993). It has been suggested that EBV may play a part in NHL associated with mild, as well as severe, immunosuppression (Tosato *et al,* 1984; Fox *et al,* 1992; Kamel *et al,* 1993).

If mild immunosuppression does increase NHL risk, might NHL trends reflect changes in the frequency of immune related medical conditions? Rates

for NHL have not risen in the wake of outbreaks of chronic fatigue syndrome (Levine *et al,* 1992). Tielsch *et al* (1987) found slightly decreased risks of NHL associated with a history of chronic infectious disease or inflammation, autoimmune disease and an index of antigenic stimulation. Cartwright *et al* (1988) reported increased risk of NHL associated with eczema and other skin conditions, kidney stones and herpes zoster. McWhorter (1988) reported that people with recurrent hives had increased risk of lymphoma, leukaemia and myeloma combined. Bernstein and Ross (1992) found decreased NHL risk associated with eczema, skin allergy, and insect allergy, whereas increased risk was associated with kidney and other infections and many common medications, including antibiotics, digitalis and corticosteriods. No effect on risk was seen for asthma or hay fever, two conditions that may be increasing in prevalence in areas with high levels of air pollution. Doody *et al* (1992) reported that NHL risk may be related to eczema, tuberculosis and bronchitis but not to hay fever. Thus, it remains unclear whether mild immune perturbations resulting from medical conditions or medications affect NHL risk.

Ionizing radiation has little or no effect on risk of NHL (Boice, 1992). The hypothesis that electromagnetic fields and other non-ionizing radiation exposures could increase risk of NHL has only weak support (Milham, 1988; Boice, 1992; Pearce and Bethwaite, 1992). There is also little evidence that alcohol or tobacco alters the risk of NHL (Brown *et al,* 1992a, b).

Many occupations have been linked to NHL risk, including farming, fishing, forestry, carpentry, construction and leather work (Cantor *et al,* 1982; Blair and Zahm, 1991; Pasqualetti *et al,* 1991; Cantor, 1992; Scherr *et al,* 1992). Contact with insecticides, pesticides, solvents, particulates and viruses may be responsible for some of the observed associations. Exposure to phenoxyacetic acid herbicides, particularly 2,4-dichlorophenoxyacetic acid, has been reported to increase risk of NHL, with relative risks ranging from 2 to 8 (Hoar *et al,* 1986; Zahm *et al,* 1990; Pearce, 1989; Zahm and Blair, 1992). Veterans exposed to herbicides in Vietnam appear not to be at increased risk of NHL (Selected Cancers Cooperative Study Group, 1990; Dalager *et al,* 1991) despite some positive reports (Namboodiri and Harris, 1991). The proportion of NHL attributed to occupation has ranged from 4% to 11% (Hartge and Devesa, 1992).

Herbicides were introduced after World War II and now are widely used in agriculture and on lawns and gardens (Zilberman *et al,* 1991). Recent estimates in the USA suggest one tenth of single family households use commercial lawn care and one fifth apply pesticides themselves (Zahm and Blair, 1992). Lawn and home use of pesticides is uncommon in less industrialized countries, but agricultural exposures may well be greater. Thus, pesticide exposure emerges as a plausible risk factor that may help explain the NHL trends, although much work needs to be done to confirm the risk of NHL associated with various pesticides and to correlate exposure levels with international trends.

Although a number of industrial agents have been linked to NHL, often

with uncertainty, the relative risks of workers are typically under 2, and must surely be lower for non-occupational exposures (Blair *et al,* 1992). Residential proximity to certain industries has been suggested as a risk factor (Linos *et al,* 1991) but further studies are needed. An ecological study found elevated NHL incidence rates in municipalities with high measures of phenoxyherbicide exposure (Vineis *et al,* 1991). Subsequently, Vineis *et al* (1992) proposed that immunotoxic effects of pesticides and solvents may potentiate viral lymphomagenesis.

In recent studies, hair dyes have been related to NHL risk (Cantor *et al,* 1988; Zahm *et al,* 1992), but the association needs to be confirmed. Although hair dye use has risen dramatically among women in the USA and other industrialized countries, it seems unlikely to contribute to the NHL trends among men around the world.

Nutritional factors have not been clearly linked to NHL, although milk, butter, liver, coffee and cola consumption have been suggested as risk factors (Franceschi *et al,* 1989; Ursin *et al,* 1990; Davis, 1992). Coffee, milk and meat consumption trends do not parallel NHL trends, but further evaluation of dietary exposures is needed.

Could the prevalence of any known or suspected risk factors have changed enough to produce the dramatic increase in NHL? Hartge and Devesa (1992) attempted to estimate the likely impact of changes in diagnostic practice and accepted risk factors on 40 year trends in NHL incidence in the USA. Over the four decades, the age adjusted rates increased 152% in men, 106% in men aged 0–64, and 147% in women. After plausible corrections for NHL cases previously diagnosed as HD, for newly recognized NHL entities and for cases related to HIV or occupation, the increases were reduced to an 80% rise for men overall, 42% for men under age 65, and a 94% rise for women overall. If environmental exposures or changes in host response explain the residual increases, they must double the risk and have risen in prevalence from 0% to 42% in men under age 65 or else have stronger effects on risk and smaller changes in prevalence.

Further investigation of a viral origin for the increase in NHL has been recommended (Essex, 1992), as have studies examining the effects of antibiotics (Kinlen, 1992), chemicals and a variety of other exposures that may alter host susceptibility (Correa, 1992). If aetiological factors explain part of the trends as suspected, substantial levels of risk and exposure have been operating around the world and should be uncovered by intensive epidemiological research, especially in conjunction with appropriate laboratory probes.

SUMMARY

Incidence of HD varies from about 0.5 per 100 000 person-years in parts of Asia to over 3 in parts of North America. In recent decades, many registries have reported slightly declining age adjusted incidence among men and

women. Some lymphomas previously diagnosed as HD now would be classified as NHL, but this shift does not explain all of the decline. When analysed by age group, incidence has decreased substantially at older ages, whereas increases have been reported among young adults in some industrial countries. Less developed countries continue to show high rates in childhood. Hodgkin's disease of the nodular sclerosis subtype has increased over time, whereas HD of mixed cellularity has declined. Improved therapy for HD has led to sharply declining mortality rates, but further understanding of the role of EBV and other possible causal agents should afford opportunities for prevention.

Non-Hodgkin's lymphoma stands out from most other malignancies because incidence and mortality rates have risen dramatically, steadily and almost universally during the past few decades. Incidence overall has been rising 3–4% per year. No sudden rise has occurred in specific birth cohorts or calendar year of diagnosis, although incidence rates have increased more steeply at older ages. Diagnosis of NHL has improved with time, perhaps beyond the ways considered herein, but has it improved so much more than diagnosis of other malignancies, and roughly simultaneously around the world? Although it appears that diagnostic improvements are partly responsible for the upward trend, it is likely that aetiological factors are playing an important part.

Infections with HIV have started to inflate NHL incidence rates further but cannot account for the striking trend already under way for several decades. Clues should be vigorously pursued to determine the role of other known viruses, immunosuppressive states, herbicides and other chemicals in the environment, and commercial products such as hair dyes. To clarify reasons for the upward trends and to take preventive action will require a better understanding of the origins of the lymphomas through epidemiological research, including interdisciplinary approaches that can identify new viruses, host-environmental interactions and lifestyle and other exposures that alter susceptibility.

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The authors are responsible for the accuracy of the references.

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